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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,453	11/22/2004	William Herman	HER1-006	9409

62879 7590 08/21/2008

HERMAN & MILLMAN
141 ADELAIDE ST. WEST
SUITE 1002
TORONTO, ON M5H 3L5
CANADA

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
08/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,453	HERMAN, WILLIAM	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10,11 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending.

2. Claims 10-11 and 14-20 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 1-9 and 12-13, drawn to a composition comprising a multispecific ligand comprising at least a first ligand binding, moiety which specifically binds to a first ligand having a first biodistribution and a second ligand binding moiety which specifically binds to a second ligand having a second biodistribution different from that of the first ligand, and wherein the affinity of the first and second ligand binding moieties are different and selected to bias the biodistribution of the multispecific ligand, the multispecific ligand is a bispecific antibody, said first ligand is a specific cell surface marker associated with cancer cell or pre-cancerous cell, and said second ligand is CXCR4, are being acted upon in this Office Action.

4. In view of the amendment filed May 15, 2008, the following objection and rejections remain.

5. The disclosure stands objected to because of the following informalities: (1) incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on page 15, line 15, and page 224 lines 14-30 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database. (2) word spacing such as the ones at page 123, line 7, page 124, line 25-28, page 125, lines 18 and 30, page 126 lines 9, 21 and 29, page 127 line 23, page 128 lines 1, 10, and 21, page 129 line 9, 13, and 25, page 139 lines 12, 18,

32, and 35, page 140, lines 14, and 35, page 141 line 34, page 142 line 8, page 145, lines 25 and 35, page 146 line 19, page 149, lines 1, 19, 27, 32, page 149, lines 8, 20 and 30, page 154 line 14, page 158 line 7, page 187, line 9. (3) pages 166-183 are different font than the rest of the specification.

6. A substitute specification is required pursuant to 37 CFR 1.125(a) because of the numerous typographical, spelling errors, font size and spacing.

A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) and a statement that the substitute specification contains no new matter must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the specification is readable.

In response, the specification stands objected to because of the embedded hyperlinks and/or other forms of browser-executable code disclosed on page 15, line 15, and page 224 lines 14-30 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database.

Further, the inconsistency in word spacing such as the ones at page 123, line 7, page 124, line 25-28, page 125, lines 18 and 30, page 126 lines 9, 21 and 29, page 127 line 23, page 128 lines 1, 10, and 21, page 129 line 9, 13, and 25, page 139 lines 12, 18, 32, and 35, page 140, lines

14, and 35, page 141 line 34, page 142 line 8, page 145, lines 25 and 35, page 146 line 19, page 149, lines 1, 19, 27, 32, page 149, lines 8, 20 and 30, page 154 line 14, page 158 line 7, and page 187, line 9 as well as different font such as pages 166-183 throughout the specification.

The spacing of the lines of the specification and different font are such as to make reading difficult. New application papers with lines 1½ or double spaced on good quality paper are required.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-9 and 12-13 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not teach how to make and use a genus of multispecific ligand as set forth in claims 1-9 and 12-13 without the structure associated with the binding specificity of such multispecific ligand or bispecific antibody to the antigen.

The specification defines the term ligand refers to any moiety, any interacting moiety including binding moiety, e.g., antibodies, receptors, etc, and bound moieties, e.g., antigens, epitopes, and including otherwise interacting moieties, e.g., chemotactic interactions, or interactions that require multiple points of interface e.g., Crosslinking or multi-component epitopes (see page 55, lines 29-37). The specification discloses a method of making bispecific antibody, minibodies diabody where one or two diabody molecules are heterodimerized by creating a fusion protein with the CL and CH1 immunoglobulin constant domains (see pages 61-62, in particular).

However, there is insufficient guidance as to binding specificity associated with the structure, i.e. amino acid sequence or nucleic acid of any and all multispecific ligand to enable one skill in the art to make such multispecific ligand for the claimed composition.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Given the lack of guidance as to the structure, one of ordinary skill in the art cannot "construct" or express any multispecific ligand without the amino acid sequence or nucleic acid sequence. Further, there is insufficient guidance with respect to the binding specificity of any first and any second moieties in the multispecific ligand, much less about the affinity of any such first and/or second affinity.

With respect to bispecific antibody, there is insufficient guidance as to the binding specificity associated with the CDRs of first binding moiety that binds to which first ligand and the CDRs of the second binding moiety that binds to which second ligand.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRS which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Kobrin et al.

Kobrin et al (J Immunology 146: 2017-2020, 1991; PTO 892) teach that a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine binding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular).

Barrios et al (J Molecular Recognition 17: 332-338, 2004, PTO 892) teach the length of the antibody heavy chain complementarity determining region (CDR3) is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and heavy chains (framework sequences) is important in maintaining their required conformation for binding and *in vivo* activity.

MacCallum et al (J. Mol. Biol. 262, 732-745, 1996; PTO 892) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

However, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody in the CDRs may adversely affect its binding activity. Likewise, fragments of the antibody may not retain the appropriate three dimensional structure necessary to foster binding activity. Moreover, a change in the DNA sequence coding for the antibody may affect the ability of the cell containing the DNA sequence to express, secrete or assemble the antibody. There are also critical framework residues which are important in positioning the CDRs for interaction with antigen or which are involved in interactions between the heavy and light chains. Therefore, it is not clear that any combination of CDR regions from either heavy or light chains or any combination of substitution, deletion, and/or addition in the CDR regions of heavy and light chain will have the asserted utility without further guidance from the specification. Further, there are no working examples in the specification as filed that the claimed composition selectively biases the biodistribution of any and all multibispecific ligand.

There is no guidance as to the structure i.e. amino acid sequence or nucleic acid of such multispecific ligand or bispecific antibody. There is a lack of *in vivo* working examples using any of such multispecific ligand or bispecific antibody for treating or targeting any cancer cells.

The specification suggests that one of skill in the art can screen for binding affinity. However, screening is not a method of how to make. As such, the specification merely extends an invitation to one of ordinary skill in the art to come up with the structure of the multispecific ligand and then test which first and second ligand to which it binds as claimed. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the specification does teach how to make and use any multispecific ligand as set forth in the claims without the structure associated with the binding specificity of such ligand or bispecific antibody. One skilled in the art would know how to create a multispecific ligand based on the teachings of the specification, One skilled in the art would know the binding specificity of individual ligands and can test for the binding specificity without undue experimentation.

Contrary to applicants' assertion that one of ordinary skill in the art would know how to make the claimed multispecific ligand without knowing which antigen and/or receptor the claimed multispecific ligand binds, one of skilled in the art cannot make and use the claimed multispecific ligand because of the lack of specific guidance as to the binding specificity of such first and second ligand binding moieties and where biodistribution is being select to bias such distribution for the claimed multispecific ligand. Screening for binding affinity is not equal to how to make, much less how to use the multispecific ligand. The instant specification does not describe the claimed invention in terms that will "enable any person skilled in the art ...to make and use" the invention. The specification merely discloses a laundry list of references and such list provides a starting point from which one of skill in the art to discover how to practice the claimed invention and does not address the specific teachings how to make and use the claimed invention. Given the enormous number of potential combinations of the first moieties, and second binding moieties, i.e., antibodies, receptors, ligands, chemokines, cytokines, etc, and the absence of further guidance and working example, the breadth of the claims, which encompass innumerable possible combination of proteins, and the amount of experimentation required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims.

9. Claims 1-9 and 12-13 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 1-2 are broadly drawn to a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

Claim 3 is broadly to a composition comprising a genus of bispecific antibody comprising a genus of first ligand binding moiety which binds to a genus of first ligand and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

Claim 4 is broadly to a composition comprising a genus of bispecific antibody comprising a genus of first ligand binding moiety which binds to a genus of first ligand and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the first and second ligand having different biodistribution and wherein the biodistribution of the multispecific ligand favors any first ligand.

Claim 5 is broadly to a composition comprising a genus of bispecific antibody comprising a genus of first ligand binding moiety which binds to a genus of first ligand and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the first and second ligand have overlapping biodistributions.

Claim 6 is broadly to a composition comprising a genus of bispecific antibody comprising a genus of first ligand binding moiety which binds to a genus of first ligand present on any first target cell population and a genus of second ligand binding moiety which specifically binds to a genus of second ligand present on a second target cell population wherein the biodistribution of the multispecific ligand favours the first target cell population.

Claim 7 is broadly drawn to a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand such as cell surface marker associated with one or more cell populations, diseased cells, or disease associated cells and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

Claim 8 is broadly drawn to a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand such as an a cell surface antigen associated with one or more cell populations, diseased cells, or disease associated cells and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

Claim 9 is broadly drawn to a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand such as an a cell surface epitope associated with one or more cell populations, diseased cells, or disease associated cells and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

Claim 12 is broadly drawn to a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand such as cell surface marker associated with cancer cell or pre-cancerous cell and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

Claim 13 is broadly drawn to a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand such as cell surface marker associated with one or more cell populations, diseased cells, or disease associated cells and a genus of second ligand binding moiety which specifically binds to a genus of second ligand such as a CXCR4 receptor wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., complete or partial structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, method of making the claimed invention, level of skill and knowledge in the art and predictability in the art

sufficient to show that applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

In this case, the specification does not reasonably provide a **written description** of (1) the structure of any multispecific ligand associated with the binding specificity and affinity of such multispecific ligand to any first ligand and any second ligand as set forth in claims 1-9 and 12, and (2) the structure of any multispecific ligand associated with the binding specificity and affinity of such multispecific ligand to any first and any second ligand such as CXCR4 receptor.

The specification defines the term ligand refers to any moiety, any interacting moiety including binding moiety, e.g., antibodies, receptors, etc, and bound moieties, e.g., antigens, epitopes, and including otherwise interacting moieties, e.g., chemotactic interactions, or interactions that require multiple points of interface e.g., Crosslinking or multi-component epitopes (see page 55, lines 29-37). The specification discloses a method of making bispecific antibody, minibodies diabody where one or two diabody molecules are heterodimerized by creating a fusion protein with the CL and CH1 immunoglobulin constant domains (see pages 61-62, in particular).

At the time of filing, Applicant is not in possession of a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution.

The specification does not adequately describe the structure of any multispecific ligand associated with the binding specificity and affinity of such multispecific ligand. This is because the structure, i.e. amino acid sequence or nucleic acid of any and all multispecific ligand to enable

one skill in the art to make such multispecific ligand is not described. Further, there is insufficient written description about the binding specificity of such multispecific ligand.

Even if the multispecific ligand is limited to bispecific antibody, the specification does not adequately describe the structure, i.e., the six CDRs of immunoglobulin heavy and light chains associated with binding specificity of such antibody, such as bispecific antibody that binds to CXCR4 receptor and/or any cell surface marker associated with one or more cell population, diseased cells, disease-associated cells, much less about the binding affinity of such multispecific ligand that favors the multispecific ligand to which cell population.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skill artisan cannot envision the detailed chemical structure of the encompassed genus of multispecific ligand and bispecific antibody that bias the biodistribution of such ligand and bispecific antibody toward which cell population expressing which first and second ligand, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. The antagonist itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

Since the specification does not disclose any specific multispecific ligand and bispecific antibody comprising a first moiety binding to a first ligand and a second moiety which binds to a second target ligand wherein the affinity for the first and second ligand binding moieties are different or wherein the first ligand binding moieties is greater than the second binding moiety, one of skill in the art would reasonably conclude that the disclosure fails to disclose the claimed composition comprising such multispecific ligand and such bispecific antibody, let alone

providing a representative number of multispecific ligand and bispecific antibody to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).* Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 1-9 and 12-13.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that not every structure of every ligand must be provided. One skilled in the art can determine sufficient ligands and binding specificities according to the teachings of the present invention.

In response, at the time of filing, application is not in possession of a composition comprising a genus of multispecific ligand comprising a genus of first ligand binding moiety which binds to a genus of first ligand and a genus of second ligand binding moiety which specifically binds to a genus of second ligand wherein the affinity of the first and second ligand binding moieties are different and the first and second ligand having different biodistribution. There is not a single multispecific ligand having different binding moieties with different affinity to bias the distribution of such multispecific ligand *in vivo* in the specification as filed.

In this case, the specification does not reasonably provide a **written description** of the binding specificity associated with the structure of any first and second binding moieties having greater affinity for first ligand than the second ligand for the claimed multispecific ligand. There is not a single multispecific ligand or bispecific antibody in the specification as filed where the first ligand binding moiety has different binding affinity (i.e., greater affinity) to which first

ligand, cell surface marker associated with one or more specific cell population, or diseased cells, or antigen or epitope on such cells than the second ligand binding moiety that binds to which second ligand. A mere listing of references wishing to obtain a multispecific ligand is not sufficient to provide possession of the claimed genus. Adequate written description requires more than a mere statement that it is part of the invention. The antagonist itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd*., 18 USPQ2d 1016. One cannot describe what one has not conceived. One of skill in the art would reasonably conclude that the disclosure fails to disclose the claimed composition comprising such multispecific ligand and such bispecific antibody, let alone providing a representative number of multispecific ligand and bispecific antibody to describe the genus for treating any diseases such as AIDS.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4, 6-9 and 12 stand rejected under 35 U.S.C. 102(b) as being anticipated by McCall et al (of record, Molecular Immunology 36: 433-446, 1999; PTO 892).

McCall et al teach various composition such as a composition comprising a multispecific ligand such as a bispecific single chain antibody C6.5 x NM3E2 bs-scFv comprising at least a first ligand binding moiety such as scFv CDRs C6.5 which binds to a first ligand such as extracellular domain of tumor-associated antigen HER2/neu covalently linked to a second ligand binding moiety such as scFv NM3E2 which binds to a second ligand such as CD16 (see entire document, page 443, col. 2, in particular). The reference bispecific C6.5 x NM3E2 bs-scFv has different affinity (see Table 1, Fig 1, in particular) and selected to bias the biodistribution of the reference bs-scFv to tumor cells expressing HER/neu (see page 444, col. 1, in particular). The reference composition further comprises a physiologically acceptable excipient such as Tris buffer or HEPES (see materials and methods, in particular). The bispecific C6.5 x NM3E2 bs-scFv has higher affinity for HER2/neu and binds CD16 expressed on neutrophils transiently (see abstract, page 443, col. 1, Discussion, in particular). The reference first and second ligands such as HER2/neu and CD16 have overlapping biodistribution such as tumor: blood or tumor: organ

(see page 442, col. 2, Table 2, page 444, col. 1, in particular). The reference HER2/neu (first ligand) is expressed on first target cell such as human breast cancer cell such as SK-OV3 and the second ligand CD16 is expressed on human neutrophils and NK cells (see abstract, page 433-343, in particular). Thus, the reference teachings anticipate the claimed invention. Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that McCall, et at. does not disclose a composition comprising a multispecific ligand comprising at least a first ligand binding moiety which specifically binds to a first ligand having a first biodistribution and a second ligand binding moiety which specifically binds to a second ligand having a second biodistribution different from that of the first ligand, and wherein the affinity of the first and second ligand binding moieties are different and selected to bias the biodistribution of the multispecific ligand.

Contrary to the applicants' assertion that McCall does not teach the claimed composition, McCall et al teach various composition such as a composition comprising a multispecific ligand such as a bispecific single chain antibody C6.5 x NM3E2 bs-scFv comprising at least a first

ligand binding moiety such as scFv CDRs C6.5 which binds to a first ligand such as extracellular domain of tumor-associated antigen HER2/neu covalently linked to a second ligand binding moiety such as scFv NM3E2 which binds to a second ligand such as CD16 (see entire document, page 443, col. 2, in particular). The reference bispecific C6.5 x NM3E2 bs-scFv has *different affinity* (see Table 1, Fig 1, in particular) and therefore inherently bias the biodistribution of the reference bs-scFv multispecific ligand to tumor cells expressing HER/neu (see page 444, col. 1, in particular). Given the overly broad specificity of the multispecific ligand in the claimed composition, the teachings of McCall et al anticipate the claimed invention.

12. Claims 1-4, 6-9, and 12 stand rejected under 35 U.S.C. 102(b) as being anticipated by Shalaby et al (of record, Clinical Immunology and Immunopathology 74(2): 185-192, 1995; PTO 892).

Shalaby et al teach a composition comprising a multispecific ligand such as a humanized bispecific $F(ab')_2$ fragment comprising a first ligand binding moiety (Fab') that binds to an epitope on CD3 and a second ligand binding moiety (Fab') that binds a cell surface tyrosine kinase receptor such as HER2 (see entire document, Preparation of humanized Bs F(ab')2 variants, in particular). The reference composition further comprises a physiological acceptable excipient such as PBS (see page 187, col. 2, second paragraph, caption of FIG 1, in particular). The affinity of the reference bispecific antibody biases the biodistribution of the reference bispecific antibody toward tumor cells (see page 189, col. 1, first paragraph, in particular). The first ligand binding moiety of the reference bispecific antibody binds to the CD3 receptor on T cells with high affinity such as a Kd of 2.49 nM, which is higher than the affinity of the second ligand binding moiety that binds to HER2 receptor on human breast cancer cells SKBR-3 such as Kd of 11.1nM (see page 188, col. 2, first paragraph, in particular). Thus, the reference teachings anticipate the claimed invention. Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673,

1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Shalaby, et al. does not disclose a composition comprising a multispecific ligand comprising at least a first ligand binding moiety which specifically binds to a first ligand having a first biodistribution and a second ligand binding moiety which specifically binds to a second ligand having a second biodistribution different from that of the first ligand, and wherein the affinity of the first and second ligand binding moieties are different and selected to bias the biodistribution of the multispecific ligand.

Contrary to the applicants' assertion that Shalaby et al does not teach the claimed composition, Shalaby et al teach a composition comprising a multispecific ligand such as a humanized bispecific $F(ab')_2$ fragment comprising a first ligand binding moiety (Fab') that binds to an epitope on CD3 and a second ligand binding moiety (Fab') that binds a cell surface tyrosine kinase receptor such as HER2 (see entire document, Preparation of humanized Bs $F(ab')_2$ variants, in particular). The reference composition further comprises a physiological acceptable excipient such as PBS (see page 187, col. 2, second paragraph, caption of FIG 1, in particular). The affinity of the reference bispecific antibody biases the biodistribution of the reference bispecific antibody toward tumor cells (see page 189, col. 1, first paragraph, in particular). The first ligand binding moiety of the reference bispecific antibody binds to the CD3 receptor on T cells with affinity such as a Kd of 2.49 nM, which is higher than the affinity of the second ligand binding moiety that binds to HER2 receptor on human breast cancer cells SKBR-3 such as Kd of 11.1nM (see page 188, col. 2, first paragraph, in particular). Given the overly broad specificity of the multispecific ligand in the claimed composition, the teachings of Shalaby et al anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over McCall et al (of record, Molecular Immunology 36: 433-446, 1999; PTO 892) in view of US Pat No. 6,949,243B1 (of record, filed Nov 22, 2000; claimed priority to provisional 60/167,519 filed Nov 24, 1999; PTO 892).

The teachings of McCall have been discussed supra.

The invention in claim 13 differs from the teachings of the reference only in that the multispecific ligand wherein the second binding moiety binds to second ligand CXCR4 receptor.

The '243 patent teaches various chemokine receptors such as CXCR4 are expressed on cancer cells such as breast cancer, head and neck, melanoma and prostate carcinoma (see Summary of invention, col. 4, lines 22-49, in particular). The '243 patent teaches various ligands that to CXCR4 receptor such as polyclonal, monoclonal, humanized, chimeric antibodies and binding fragment thereof for use as targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells (see col. 6-9, in particular). The '243 patent teaches receptor targeting may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing, etc (see paragraph bridging col. 14 and 15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a multispecific ligand comprising at least a binding moiety such as anti-CD16 that binds to a second cell surface target such as human CD16 expressed on neutrophils or NK cells as taught by McCall and antibody that binds to any chemokine receptor such as CXCR4 as taught by the '243 patent by substituting one of the ligand binding domain that binds to HER2/Neu2 that expressed on tumor cell as taught by McCall. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '243 patent teaches CXCR4 receptors are expressed on tumor cells such as breast cancer, head and neck and melanoma and antibody that binds to such receptor expressed on tumor cells is

useful as a targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells and may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing (see paragraph bridging col. 14 and 15, in particular). McCall et al teach bs-scFv is capable of redirecting CD16 positive cells toward tumor cells expressing the HER2/neu2 thereby lysis of tumor cells (see abstract, page 444, col. 2, in particular). Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that McCall, et al. does not disclose all the required elements of the presently pending independent claim. Therefore, combination of McCall, et al. with the '243 patent does not make up for the deficiencies of McCall, et al. alone.

Contrary to the applicants' assertion that McCall does not teach the claimed composition, McCall et al teach various composition such as a composition comprising a multispecific ligand such as a bispecific single chain antibody C6.5 x NM3E2 bs-scFv comprising at least a first ligand binding moiety such as scFv CDRs C6.5 which binds to a first ligand such as extracellular domain of tumor-associated antigen HER2/neu covalently linked to a second ligand binding

moiety such as scFv NM3E2 which binds to a second ligand such as CD16 (see entire document, page 443, col. 2, in particular). The reference bispecific C6.5 x NM3E2 bs-scFv has *different affinity* (see Table 1, Fig 1, in particular) and therefore inherently bias the biodistribution of the reference bs-scFv multispecific ligand to tumor cells expressing HER/neu (see page 444, col. 1, in particular).

The invention in claim 13 differs from the teachings of the reference only in that the multispecific ligand wherein the second binding moiety binds to second ligand CXCR4 receptor.

The '243 patent teaches various chemokine receptors such as CXCR4 are expressed on cancer cells such as breast cancer, head and neck, melanoma and prostate carcinoma (see Summary of invention, col. 4, lines 22-49, in particular). The '243 patent teaches various ligands that bind to CXCR4 receptor such as polyclonal, monoclonal, humanized, chimeric antibodies and binding fragment thereof for use as targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells (see col. 6-9, in particular). The '243 patent teaches receptor targeting may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing, etc (see paragraph bridging col. 14 and 15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a multispecific ligand comprising at least a binding moiety such as anti-CD16 that binds to a second cell surface target such as human CD16 expressed on neutrophils or NK cells as taught by McCall and antibody that binds to any chemokine receptor such as CXCR4 as taught by the '243 patent by substituting one of the ligand binding domain that binds to HER2/Neu2 that expressed on tumor cell as taught by McCall. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '243 patent teaches CXCR4 receptors are expressed on tumor cells such as breast cancer, head and neck and melanoma and antibody that binds to such receptor expressed on tumor cells is useful as a targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells and may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing (see paragraph bridging col. 14 and 15, in particular). McCall et al teach bs-scFv is capable of redirecting CD16 positive cells toward tumor cells expressing the HER2/neu2 thereby lysis of tumor cells (see abstract, page 444, col. 2, in

particular). Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

15. Claims 1-5 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Shalaby et al (of record, Clinical Immunology and Immunopathology 74(2): 185-192, 1995; PTO 892) in view of US Pat No. 6,949,243B1 (of record, filed Nov 22, 2000; claimed priority to provisional 60/167,519 filed Nov 24, 1999; PTO 892).

The teachings of Shalaby et al have been discussed supra.

The invention in claim 5 differs from the teachings of the reference only in that the multispecific ligand wherein the first and second ligands have overlapping biodistributions.

The invention in claim 13 differs from the teachings of the references only in that the multispecific ligand wherein the second binding moiety binds to second ligand CXCR4 receptor instead of HER2 receptor.

The '243 patent teaches various chemokine receptors such as CXCR4 are expressed on cancer cells such as breast cancer, head and neck, melanoma and prostate carcinoma (see Summary of invention, col. 4, lines 22-49, in particular). The '243 patent teaches various ligands that to CXCR4 receptor such as polyclonal, monoclonal, humanized, chimeric antibodies and binding fragment thereof for use as targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells (see col. 6-9, in particular). The '243 patent teaches receptor targeting

may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing, etc (see paragraph bridging col. 14 and 15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a multispecific ligand comprising at least a binding moiety such as anti-CD3 that binds to human CD3 expressed on T cells as taught by Shalaby and antibody that binds to any chemokine receptor such as CXCR4 as taught by the '243 patent by substituting one of the ligand binding domain that binds to HER2/Neu2 that expressed on tumor cell as taught by Shalaby et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '243 patent teaches CXCR4 receptors are expressed on tumor cells such as breast cancer, head and neck and melanoma and antibody that binds to such receptor expressed on tumor cells is useful as a targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells and may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing (see paragraph bridging col. 14 and 15, in particular). Shalaby et al teach bispecific F(ab')2 antibody has the ability to target CD3 positive T cells toward tumor cells expressing the HER2 antigen and thereby inhibits the proliferative activities of these tumor cells (see abstract, in particular). Claim 5 is included in this rejection because CXCR4 expressed on tumor cells tended to metastasize to lymph nodes, which has overlapping biodistributions as the chemokine secreted by leukocytes in the lymph nodes. Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement

rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Shalaby, et al. does not disclose all the required elements of the presently pending independent claim. Therefore, combination of Shalaby, et al. with the '243 patent does not make up for the deficiencies of Shalaby, et al. alone.

Contrary to the applicants' assertion that Shalaby et al does not teach the claimed composition, Shalaby et al teach a composition comprising a multispecific ligand such as a humanized bispecific $F(ab')_2$ fragment comprising a first ligand binding moiety (Fab') that binds to an epitope on CD3 and a second ligand binding moiety (Fab') that binds a cell surface tyrosine kinase receptor such as HER2 (see entire document, Preparation of humanized Bs F(ab')2 variants, in particular). The reference composition further comprises a physiological acceptable excipient such as PBS (see page 187, col. 2, second paragraph, caption of FIG 1, in particular). The affinity of the reference bispecific antibody biases the biodistribution of the reference bispecific antibody toward tumor cells (see page 189, col. 1, first paragraph, in particular). The first ligand binding moiety of the reference bispecific antibody binds to the CD3 receptor on T cells with high affinity such as a Kd of 2.49 nM, which is higher than the affinity of the second ligand binding moiety that binds to HER2 receptor on human breast cancer cells SKBR-3 such as Kd of 11.1nM (see page 188, col. 2, first paragraph, in particular).

The invention in claim 13 differs from the teachings of the reference only in that the multispecific ligand wherein the second binding moiety binds to second ligand CXCR4 receptor.

The '243 patent teaches various chemokine receptors such as CXCR4 are expressed on cancer cells such as breast cancer, head and neck, melanoma and prostate carcinoma (see Summary of invention, col. 4, lines 22-49, in particular). The '243 patent teaches various ligands that to CXCR4 receptor such as polyclonal, monoclonal, humanized, chimeric antibodies and binding fragment thereof for use as targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells (see col. 6-9, in particular). The '243 patent teaches receptor targeting

may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing, etc (see paragraph bridging col. 14 and 15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a multispecific ligand comprising at least a binding moiety such as anti-CD16 that binds to a second cell surface target such as human CD16 expressed on neutrophils or NK cells as taught by McCall and antibody that binds to any chemokine receptor such as CXCR4 as taught by the '243 patent by substituting one of the ligand binding domain that binds to HER2/Neu2 that expressed on tumor cell as taught by McCall. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '243 patent teaches CXCR4 receptors are expressed on tumor cells such as breast cancer, head and neck and melanoma and antibody that binds to such receptor expressed on tumor cells is useful as a targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells and may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing (see paragraph bridging col. 14 and 15, in particular). McCall et al teach bs-scFv is capable of redirecting CD16 positive cells toward tumor cells expressing the HER2/neu2 thereby lysis of tumor cells (see abstract, page 444, col. 2, in particular). Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the

issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

16. Claims 1-5 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bruhl et al (of record, J Immunology 166: 2420-2426, Feb 2001; PTO 892) in view of US Pat No. 6,949,243B1 (of record, filed Nov 22, 2000; claimed priority to provisional 60/167,519 filed Nov 24, 1999; PTO 892), US Pat No. 6,197,578 (of record, filed Jan 30, 1997; PTO 892) and US Pat No. 6,488,930 (of record, filed Jan 15, 1999; PTO 892).

Bruhl et al teach a composition comprising a bispecific ligand such as bispecific antibody that has a first binding moiety such as single chain fragment (CRR5 VL/CRR5 VH) that binds to CRR5 and a binding moiety such as single-chain fragment directed against CD3 (CD3 VH/CD3 VL) (see Figure 1, page 2421, col. 2, construction and expression of the bispecific single chain Ab anti-CCR5-anti-CD3, in particular). The reference bispecific antibody has one arm that binds to CD3 antigen or marker expressed on T cells while the other arm of the antibody binds to CCR5 receptor expressed on cell such as human monocytes (see page 2422, col. 2, in particular). The reference bispecific single-chain antibody could potentially be applied to deplete CCR5-positive T cells and monocytes from inflamed joints of patient with arthritis (see page 2423, col. 1, in particular) or HIV-infected cells positive for CCR5 (see page 2424, col. 2, page 2425, col. 2, in particular). Binding of the bispecific antibody to CD3+ T cells and CCR5+ target cells results in cross-linkage of CD3, activation of effector T cells and lysis of CCR5 positive target cells (see page 2421, caption of Fig 1, in particular). The reference binding moiety of single chain antibody fragment (CRR5 VL/CRR5 VH) that binds to CRR5 and a binding moiety such as single-chain fragment directed against CD3 (CD3 VH/CD3 VL) which come from two different single antibodies obviously have different binding affinity. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Further, the low affinity of the reference single chain fragment from anti-CD3 and the high affinity of the reference anti-CCR5 are property of the reference bispecific antibody.

The invention in claim 5 differs from the teachings of the reference only in that the multispecific ligand wherein the first and second ligands have overlapping biodistributions.

The invention in claim 13 differs from the teachings of the reference only in that the multispecific ligand wherein the second binding moiety binds to second ligand CXCR4 receptor instead of CXCR5 receptor.

The '243 patent teaches chemokine receptor CXCR4 is expressed on tumor cells such as breast cancer, head and neck, melanoma, and prostate carcinoma and has been implicated in liver, lung and lymph node metastasis (see Summary of invention, col. 4, lines 22-49, in particular). The '243 patent also teaches various ligands that bind to such CXCR4 receptors expressed on cancer cells such as polyclonal, monoclonal, humanized, chimeric antibodies and binding fragment thereof for use as targeting moiety to bring chemotherapeutic agent to CXCR4 receptors bearing cells (see col. 6-9, in particular). The '243 patent teaches receptor targeting may allow for specific administration of therapeutic drugs, e.g., by localized attraction, activation, absorption or activation of killing, etc (see paragraph bridging col. 14 and 15, in particular).

The '578 patent teaches CXCR4 is a cell surface receptor for HIV infection and various antibodies such as monoclonal, humanized and binding fragment such as Fv that binds to CXCR4 expressed on T cells that blocks HIV envelopment mediated fusion associated with HIV entry into human CD4 positive cells (see col. 3, lines 18-30, col. 9, lines 53-65, col. 11-12, in particular). The reference antibodies also useful as a target for drug delivery system (see col. 17, lines 10-12, in particular).

The '930 patent teaches CCR4 receptor is expressed on human T cells, monocytes and endothelial cells (see col. 15, lines 23-25, particular). The '930 patent further teaches various multispecific ligand such as bispecific antibody that binds to different epitope of CXCR4 (see col. 7, line 45-53, in particular). The reference CCR4 has overlapping distribution with CD3 on T cells.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute one of the binding moiety that binds to CXCR5 in the multispecific ligand or bispecific antibody anti-CXCR5-anti-CD3 of Bruhl et al for the binding moiety that binds to CXCR4 as taught by the '243 patent, or the '578 patent or the '930 patent to form a multispecific ligand that binds to CXCR4 and CD3. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do this because bispecific antibody that binds to CCR4 and CD3 would target the cells

expressing CXCR4 to CD3 positive T cells or attracting leukocytes to the tumor as taught by the '243 patent (see col. 9, lines 1-2, paragraph bridging col. 11 and 12, in particular). Bispecific antibody that binds to CXCR4 and CD3 can also target T cells expressing CD3 to HIV infected cells because CXCR4 is a cell surface receptor for HIV infection and antibodies to CXCR4 are useful for targeting drug or cells to such infected cells as taught by the '578 patent (see col. 17, lines 10-12, in particular). Bruhl teach bispecific single-chain antibody could potentially be applied to deplete T cells and monocytes from inflamed joints of patient with arthritis (see page 2423, col. 1, in particular) or HIV-infected cells positive for chemokine receptor such as CXCR5 (see page 2424, col. 2, page 2425, col. 2, in particular). Binding of the bispecific antibody to CD3+ T cells and CCR5+ target cells results in cross-linkage of CD3, activation of effector T cells and lysis of CCR5 positive target cells (see page 2421, caption of Fig 1, in particular). Because the teachings of the specification do not appear to add anything further to the teachings of the prior art, if the specification is enabling, the prior art is also enabling, and if the prior art is not enabling, neither is the specification. The burden is thus placed on the applicant to point out the teachings of the specification to go beyond those of the prior art. The policy interests of compact prosecution are also served if the examiner makes both the prior art rejection and the enablement rejection in first instance. In a case such as this, where only the prior art was made, if applicant can show that the reference is not enabling and reference is based on "obvious to try" standard, see In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988), the examiner would be in the position of having to drop the art rejection, only to reopen prosecution to make the enablement rejection. The converse is also true if the examiner had made only the enablement rejection, and then upon a showing that the specification is enabling, the enablement rejection may have been mooted but the art rejection would have to be made. If both rejections were made from the beginning, however, the applicant knows where the issues lie and can focus his or her resources on demonstrating why the teachings of the specification go beyond the teachings of the prior art.

Applicants' arguments filed May 15, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Bruhl, et al. does not disclose the required elements of the presently pending independent claim. Therefore, combination of Bruhl, et al. with the '243 patent does not make up for the deficiencies of Bruhl, et al. alone.

Contrary to applicants' assertion that Bruhl, et al. does not disclose the required elements of the presently pending independent claim, independent claim 1 recites a composition comprising a multispecific ligand comprising a at least a first ligand binding moiety which specifically binds to a first ligand having a first biodistribution and a second ligand binding moiety which specifically binds to a second ligand having a second biodistribution different from that of the first ligand, and wherein the affinity of the first and second ligand binding moieties are different and selected to bias the biodistribution of the multispecific ligand. Independent claim merely requires that the multispecific ligand binds to at least two different targets with different affinity.

Bruhl et al teach a composition comprising a bispecific ligand such as bispecific antibody that has a first binding moiety such as single chain fragment (CRR5 VL/CRR5 VH) that binds to CRR5 and a binding moiety such as single-chain fragment directed against CD3 (CD3 VH/CD3 VL) (see Figure 1, page 2421, col. 2, construction and expression of the bispecific single chain Ab anti-CCR5-anti-CD3, in particular). The reference bispecific antibody has one arm that binds to CD3 antigen or marker expressed on T cells while the other arm of the antibody binds to CCR5 receptor expressed on cell such as human monocytes (see page 2422, col. 2, in particular). The reference bispecific single-chain antibody could potentially be applied to deplete CCR5-positive T cells and monocytes from inflamed joints of patient with arthritis (see page 2423, col. 1, in particular) or HIV-infected cells positive for CCR5 (see page 2424, col. 2, page 2425, col. 2, in particular). Binding of the bispecific antibody to CD3+ T cells and CCR5+ target cells results in cross-linkage of CD3, activation of effector T cells and lysis of CCR5 positive target cells (see page 2421, caption of Fig 1, in particular). The reference binding moiety of single chain antibody fragment (CRR5 VL/CRR5 VH) that binds to CRR5 and a binding moiety such as single-chain fragment directed against CD3 (CD3 VH/CD3 VL) which come from two different single antibodies obviously have different binding affinity. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

17. No claim is allowed.

18. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Examiner, Art Unit 1644
August 15, 2008